AIDS:
MEDICAL AND SCIENTIFIC ASPECTS

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ISSUE DEFINITION

Acquired Immune Deficiency Syndrome (AIDS) was first described in the United States in the summer of 1981 and was initially associated with cases of *Pneumocystis carinii pneumonia* (PCP) and Kaposi's sarcoma (KS) in young homosexual men who were also immunocompromised. The first case of AIDS in Canada was reported in February 1982. Since then the incidence of AIDS has grown significantly. **Statistics compiled by the World Health Organization and presented at the XI International Conference on AIDS (July 1996, Vancouver) indicated that worldwide almost 22 million people are infected with HIV, and approximately 8,500 new cases occur daily. The vast majority of those infected (90%) live in the developing world, particularly in sub-Saharan Africa, southeast Asia and the Asian sub-continent. It has been estimated that 4.5 million people have already died from AIDS; however, exact numbers are difficult to obtain because of under-diagnosis, incomplete reporting and reporting delays in many countries.**

As its name suggests, AIDS involves the breakdown of the body's immune system, leaving the victim vulnerable to unusual and fatal diseases. The virus that is now known to cause AIDS, the human immunodeficiency virus, or HIV, was discovered in 1983. HIV is not highly contagious and its transmission is easily preventable, but prevention is predicated on behavioural change among populations at risk. The virus is unusual; it has a very high mutation rate; and, although its mode of action is not fully understood, it is the subject of intense research scrutiny. An effective vaccine against HIV is not expected in this century and, until recently, no effective therapies existed. In mid-1996, the results of a number of clinical trials investigating the effect of mixtures of anti-HIV drugs were reported.

* The original version of this Current Issue Review was published in November 1993; the paper has been regularly updated since that time.

Early observations show that drug "cocktails" of three or more drugs can overcome the rise of drug-resistant mutants, and in many cases HIV concentrations in the blood have fallen below the level of detection. It is too soon to say that a cure for HIV/AIDS is at hand; however, it now appears that it may be possible to transform HIV disease into a chronic, controllable condition.

BACKGROUND AND ANALYSIS

In the decade and a half that has passed since the identification of AIDS, many advances have been made in understanding the disease, how it is spread, and how it may be prevented. The disease will be discussed under the following headings: Epidemiology of HIV/AIDS; the human immunodeficiency virus (HIV); the immune system and the etiology of HIV infection; associated diseases; HIV vaccines; and anti-HIV drugs.

A. Epidemiology of HIV/AIDS

Since the first AIDS case was diagnosed in Canada in 1982, the disease has spread widely. By 30 June 1996, 13,810 Canadians had been diagnosed with full-blown AIDS and 72.2% (9,969) of those persons had died. Health Canada states that the significant delay in the reporting of AIDS cases, together with under-reporting, affects the accuracy of the figures quoted above. It has been calculated that, as of 31 December 1995, the cumulative number of AIDS cases in Canada was 17,114. Following initial infection, HIV disease is characterized by a long asymptomatic period that can last for 10 years or more before full-blown AIDS is manifested. It has been estimated that, as of mid-1996, between 30,000 and 45,000 Canadians were HIV^+; or, expressed in another way, approximately one out of every 666 to 1,000 Canadians is currently infected with HIV.

Health Canada's *Quarterly Surveillance Update: AIDS in Canada*, July 1996, allocates all reported Canadian AIDS cases to an exposure/risk category. As of 30 June 1996, 73.8% of all AIDS cases were due to homosexual activity, while 4.3% of

cases occurred among men who identified a combination of homosexual activity and intravenous drug use as risk factors. Perinatal transmission (children under 15 years of age) accounted for 0.8% of cases. The balance of AIDS cases (21.2%), which occurred among individuals self-identifying as heterosexual, were allocated to the following risk/exposure categories: sexual contact, 9.5%; no identified risk factor, 4.3%; intravenous drug use, 3.8%; blood-clotting factor recipient, 1.8%; blood recipient, 1.7%; and occupational exposure, $<0.1\%$.

The above data serve only as a snapshot of the Canadian HIV epidemic a decade ago; they do not identify which Canadian groups are being infected today. Only in Canada and the developed nations of Europe and Australasia does AIDS remain a disease where the majority of those afflicted are gay. The incidence of new HIV infections among Canadian gay men has fallen, with the most significant decrease taking place among older gay men who have witnessed the death of friends and loved ones. Unfortunately, young gay men are less likely to practise safe sex and they continue to have a relatively high rate of infection. As the epidemic in the gay population slackens, it is intensifying among young heterosexuals. In Canada, the median age of HIV infection has fallen to 23 years from 32 in the early 1980s.

In the United States, AIDS ceased being primarily a disease of gay men in the early 1990s. Data from the United States Centers for Disease Control and Prevention show that the proportion of new cases reported among homosexual/bisexual men decreased from 47.3% in 1993 to 43.3% in 1994. At the same time, the rate of infection increased among women and minority groups. Women accounted for 18.1% of total AIDS cases in 1994, up from 16.2% in 1993, while over the same period the percentage of American Blacks with AIDS increased from 36.1% to 39% of total new cases and the percentage of Hispanic Americans with AIDS increased from 17.7 to 18.7%. For Americans aged 25 to 44, AIDS is the leading cause of death for men and black women and the third major cause of death for white women. In England and Wales, AIDS projections prepared by the government indicate that the number of new cases among

homosexual and bisexual males will drop by 7%, but there will be a rise of 29% among intravenous drug users and a 25% increase due to heterosexual transmission of the virus. It is considered likely that similar trends will follow in Canada.

Sexual intercourse is the principal means of HIV transmission. Unprotected anal or vaginal intercourse poses the greatest risk of infection as the epithelium tissue of both the vagina and anus/rectum contain cells that are susceptible to invasion by HIV. Scientific studies have shown that in heterosexual transmission of HIV, women are at least twice as susceptible as men; however, lack of circumcision increases the risk for men. Oral sex is believed to be a less risky sexual practice as viral entry is limited to access through oral cuts, abrasions or inflamed areas; however, HIV has been found capable of infecting Langerhans cells present on tonsil epithelium tissue. The virus is destroyed by stomach acids. The use of condoms for all sexual acts involving the exchange of body fluids significantly reduces the risk of HIV transmission.

Injection drug use involving shared needles also is a high-risk activity. Although only 3.8% of all AIDS cases diagnosed to 30 June 1996 were directly attributable to intravenous drug use, it is believed that this means of transmission is increasing in Canada's major urban centres. Canadian studies have shown that low-income inner-city residents with unstable housing are twice as likely to become infected with HIV than are wealthier drug users. It has also been observed that people who inject cocaine more than four times a day are 2.4 times more likely to become infected than are those who inject other drugs. In the United States, intravenous drug use is a major cause of new HIV infections. A February 1995 analysis conducted by the United States Centers for Disease Control and Prevention found that approximately 75% of the 40,000 newly infected with HIV in the United States in 1994 "self-medicated" with illegal drugs.

The AIDS virus can be transmitted in whole blood and blood products. Factor VIII, a coagulation product originally prepared from blood plasma, has been responsible for a large number of HIV infections. Approximately 1,200 Canadians were infected by HIV from contaminated blood and blood products in the 1980s. By 1 November 1985, the Canadian Red

Cross had fully instituted testing of all donated blood for HIV antibodies. Earlier, the Red Cross had instituted donor screening to eliminate persons in high-risk groups. The Canadian blood system now is as safe as any in the world. There remains a slight possibility of a unit of donated blood being contaminated by HIV because there is a delay of several weeks between the time a person is infected by the virus and the production of detectable antibodies in the blood. Blood products used by hemophiliacs are now regarded as safe from HIV infection because they have been subjected to heat treatment.

Infants born to mothers who are infected with HIV are at risk of contracting the virus. Mother-to-infant transmission of HIV - "perinatal transmission" - may occur in three ways: (1) infection *in utero* in cases where the virus moves across the placenta; (2) exposure of the baby to infectious blood and vaginal secretions during labour and delivery; (3) postpartum transmission through breast-feeding. The rate of infection varies considerably, but may be as low as 13% or as high as 40%. **In an American study, the incidence of perinatal transmission was reduced from 25.5% to 8.3% when AZT was administered to HIV^+ women during pregnancy and delivery and to newborns for eight weeks after birth. It is believed that further improvement can be achieved by means of combination therapy using three or more anti-HIV drugs. By 30 June 1996, 111 cases of perinatal transmission of HIV progressing to AIDS had been recorded in this country.**

Occupational transmission of HIV is of greatest concern in the medical and dental professions and, to some extent, also in areas of emergency assistance where persons come into contact with blood. HIV transmission has occurred in hospitals, usually through "needle-stick" injuries with contaminated syringes. Invasive surgical procedures also involve some risk of transmission through cuts caused by surgical instruments or bone fragments, but the incidence of infection by this means is very low. The transmission of HIV from a health-care worker to a patient has not been recorded.

The transmission of HIV by dentists to patients has been given prominence as a result of the case of a (now-deceased) Florida dentist who may have infected as many as five patients. Dentistry is not thought to be a major risk to the public, however, and procedures have been developed to sterilize dental equipment to protect patients. As in the medical profession, the

risk is greater for dentists and their assistants who treat HIV-infected persons, but this risk is regarded as very small.

The AIDS virus has been isolated in many body fluids, including saliva, but the infectivity of saliva is believed to be extremely low and transmission of HIV by this route is very low-risk, if it exists at all.

B. The Human Immunodeficiency Virus (HIV)

HIV is unlike most of the viruses that infect human beings in that it is a retrovirus whose genetic material is ribonucleic acid (RNA), rather than deoxyribonucleic acid (DNA). There are two major types of HIV: HIV-l is the commonest strain worldwide, while HIV-2 is prevalent in West Africa. Of the two, HIV-l produces the more severe disease. **To date, nine genetically distinct subtypes of HIV have been identified and designated subtypes A though H, and O.**

HIV is the most studied virus in history but much remains to be learned about it. A single HIV virus particle, or *virion*, is roughly spherical in shape. It has an outer coat, or *envelope*, consisting of a double layer of lipid (fat) molecules. The envelope is studded with proteins. Some of these are of human origin and are known as *major histocompatibility complex* (MHC) protein molecules, which are important components of the human immune system.

The virion envelope also has numerous protein "spikes," each of which contains a protein called gp120 on the outside and gp41 embedded in the envelope. The prefix "gp" stands for glycoprotein, meaning that the proteins are linked to sugars. The number refers to the mass of the protein. The gp120 envelope glycoprotein is derived from a precursor molecule called gp160. The gp120 protein is known to bind tightly to the CD4 molecule on the surface of immune cells, thus facilitating entry of HIV into the cell. Recent research has suggested that a second protein on the cell surface, an enzyme designated CD26, may serve as the actual entry point for HIV into the cell. Within the gp120 protein is a loop structure called the "V3 loop" and this is believed to be important in the infective process of HIV. Two other proteins have been identified inside the envelope, and designated p17 and p24. The core, or *capsid*, of the virion contains the genetic material of the virus, in the form of two strands of RNA. A number of enzymes essential to the infective cycle of HIV have been identified. **These are described in detail in a later section.**

C. The Immune System and the Etiology of HIV Infection

A major impediment to a full understanding of the role of HIV in the development of AIDS is the fact that the functioning of the human immune system is still incompletely understood. A brief discussion of the immune system follows.

The human immune system consists of two sub-systems: *humoral immunity* and *cell-mediated immunity*. Humoral immunity is based on the production of antibodies by B lymphocytes, or B cells, which are produced in the bone marrow and circulate in the blood stream. The B cells are extremely versatile and, in total, represent millions of antibody genes which direct the production of equal numbers of different antibodies. These lymphocytes, carrying any one of millions of different antibodies on their individual cell surfaces, constantly roam the body, ready to meet an invading *antigen*. (An antigen is a foreign protein or carbohydrate toxin, which may be produced by a pathogenic organism.) When an antigen meets a B cell carrying a matching antibody, that B cell is stimulated to divide rapidly and to secrete large numbers of antibodies to attack the invader. The antibody need not match the antigen exactly to be effective.

Cell-mediated immunity involves a type of lymphocyte, known as the T-cell, that originates in the thymus gland. Unlike a B cell, a T-cell cannot "see" the entire antigen, but receptors on its cell surface recognize protein fragments of antigens called peptides. These peptides, which are short linear sequences of amino acids, may even include the inner part of a microbe's structure. A major histocompatibility complex (MHC) protein molecule processes and "presents" the antigen fragment to the T-cell.

T-cells comprise two sub-populations, the CD4 helper and CD8 killer T-cells. The latter also are known as "cytotoxic T-cells" because they literally kill infected cells, thus limiting the spread of a virus. The CD4 helper T-cells respond to the chemical signal from the antigen fragment on the MHC protein and produce a large amount of chemicals called cytokines (or lymphokines). Interferons and interleukins are two of the various classes of cytokines produced. These chemicals stimulate the immune system and the inflammatory response of body tissue that is a part of the immune reaction.

The *complement system* is another important part of the immune system. This sub-system involves the interaction of more than 18 protein fractions which augment the body's immune defences when antibodies combine with invading antigens. Among other things, the complement system facilitates the *lysis* (break-up) of cells of invading pathogens.

The B and T-lymphocytes form a tightly interwoven system which has positive and negative feedback loops. The T-cells stimulate the B cells into an active state where they divide rapidly and produce large quantities of antibodies. In turn, the B cells process antigens into a form to which T-cells most readily respond, stimulating the T-cells into an active state.

Some understanding of the immune system is necessary in a discussion of AIDS because the dominant theory of the disease is that the CD4 T-lymphocytes are affected by the virus, producing functional abnormalities and reduced numbers of cells, leading eventually to the profound immunosuppression that characterizes advanced HIV disease. Other cell types, notably large scavenger cells called *macrophages*, are also infected by HIV, and these may serve as important reservoirs of HIV outside the blood, and as carriers of the virus to other organs (the "Trojan horse" effect).

It is generally accepted that HIV infection proceeds through a number of stages leading up to the condition known as AIDS. In 50 to 70% of patients with primary HIV infection, after three to six weeks an acute syndrome develops which is similar to mononucleosis and is marked by fever and general malaise. There is also a high level of *viremia* (virus in the blood) at this time.

Within a week to three months after initial infection, the body mounts an immune response to HIV. At the same time, it is possible that the virus becomes widely disseminated in the body, particularly in the lymphoid organs. The immune reaction results in a large decline in viremia but is unable to suppress HIV reproduction completely. The virus becomes almost undetectable in the peripheral blood cells, but remains detectable in the lymph nodes.

The mechanism(s) leading to the dysfunction and decline of CD4 T-cells is not well understood. The simplest hypothesis is that the T-cells are directly killed by the virus after infection. It has been shown also, in vitro, that an infected T-cell will fuse with a number of uninfected cells to form clusters called *syncytia*, a process which leads to the death of all the affected cells. Syncytia formation has rarely been seen *in vivo*, however.

CD4 T-lymphocytes also may be killed through an HIV-specific immune response involving both the humoral and cellular sub-systems. A number of viral proteins have been identified which stimulate antibody formation; HIV-infected T-cells that express these proteins on their surfaces may be selectively killed by cytotoxic T-cells. The immune system also may be disrupted without actual cell death: infected cells may not function properly, the result being a

compromised immune system. It has also been hypothesized than some sort of *auto-immune reaction* may be causing the death of the CD4 T-cells.

There is evidence that a significant number of individuals infected by HIV do not progress to AIDS; in some studies, about half the patients remain free of AIDS 10 years after becoming infected by the virus. One study in San Francisco found that 8 % of men infected for between 10 and 15 years remain clinically normal, exhibiting only minor abnormalities of the blood and immune systems. A research group in Britain suggests that up to 25% of patients infected with HIV will survive for 20 years without developing AIDS.

There is evidence that "viral burden" - the amount of virus in the body - is an important factor in progression to AIDS. Patients with a high viral burden, both initially and as the infection continues, seem to progress more rapidly to AIDS. Why some patients have a higher viral burden than others is not known, but the answer to that question may produce important insights into the etiology of the disease and could point the way to improved therapies.

In summary, there are a number of hypotheses about how HIV produces the pathogenic events that eventually lead to AIDS, but there is no completely satisfactory explanation as yet. The emerging majority view of AIDS is that the disease is caused by a progressive HIV burden in the infected person, involving an incompletely effective activation of the immune system, followed by the eventual destruction of that system by the virus.

D. Associated Diseases

It is now recognized that HIV infection leads to a continuous disease process that starts with the initial exposure and terminates in the advanced forms of immune deficiency, the state typically known as AIDS. Death results from the complex interactions between the HIV infection itself and the secondary opportunistic infections and cancers that are commonly associated with the syndrome.

The first stage of infection is known as the "acute retroviral syndrome" and is characterized by fevers, pharyngitis, headache, malaise and a rash. The symptoms are often mistaken for influenza or infectious mononucleosis. This phase begins about one to three weeks after infection and may last for one to two weeks. During this period, there is a burst of viremia in

the patient, who is now infective. It is important therefore that counselling be initiated immediately to prevent HIV transmission.

In the next stage of the disease, most patients enter a period of "clinical latency." In a large study of homosexual men, the median time from estimated initial infection to the development of full-blown AIDS was 10.8 years. This period varied from as little as 12 months to more than 11 years. In fact, the virus is not really inactive during this period, so the term latency is not really appropriate. Virtually all patients suffer a gradual deterioration of their immune system, particularly depletion of CD4 T-cells in the peripheral blood, and *lymphadenopathy* - swelling of the lymph nodes - typically occurs at this time.

In January 1995, a review article on the population dynamics of HIV in infected persons suggested that the long period of "clinical latency" associated with HIV/AIDS is a period of great activity during which cells are being infected and dying at a high rate and in large numbers. A "steady-state model" is suggested, during which infection, cell death, and cell replacement are in balance. This further suggests that the virus goes through an extraordinarily large number of replication cycles, a turnover that drives both the pathogenic process and the development of great genetic variation within the virus. The great accumulation of mutations accounts for the resistance that invariably develops to antiviral drugs.

The next stage of the disease is called "early symptomatic HIV disease." This designation has largely replaced the older "AIDS-related complex" (ARC) terminology. In this stage, the CD4 T-cell count has dropped significantly, and there is an increase in infectious diseases, although these are usually not life-threatening. A variety of chronic or intermittent symptoms may occur, and almost every organ system may be affected. Among the observed symptoms are: fever, night sweats, chronic diarrhoea, fatigue, minor oral infections, and headache.

Another factor that can be important in this phase is the development of adverse effects to antiretroviral drugs such as zidovudine (AZT). At this stage also, the virus may become increasingly resistant to such drugs.

In the late symptomatic stage of HIV disease, the CD4 T-cell count declines even further, and the infection rate for serious opportunistic diseases increases. Antibiotics are available to treat most diseases effectively, but these drugs often have side effects, and there is a risk of drug

resistance by the various pathogens. *Pneumocystis carinii* pneumonia (PCP) is common during this stage but is susceptible to treatment. Treatments for other infections including cryptococcal meningitis, cytomegalovirus (CMV) retinitis, central nervous system toxoplasmosis, and *Mycobacterium avium-intracellulare* tuberculosis are under development or in the experimental stage.

The final stage of the illness is familiarly referred to as "full-blown AIDS." Some medical workers prefer "advanced HIV disease" as more appropriate. In this stage, the CD4 T-cell count drops to below 50 cells/ml and the probability of death rises greatly. Opportunistic diseases remain as the greatest threat for morbidity and mortality. Careful and regular expert medical care is essential at this stage.

E. HIV Vaccines

Vaccines are the most cost-effective means of reducing infectious disease and the ideal solution to the HIV/AIDS epidemic would be an effective and affordable vaccine for general use in all countries and among all population groups. Although HIV transmission is almost completely preventable through the use of appropriate prophylaxis, this approach requires major behavioural modification in the areas of sexual activity and intravenous drug abuse, where this is notoriously difficult to achieve. There is a very active international vaccine research program and currently more than 20 experimental AIDS vaccines are in various stages of human testing.

When HIV was first discovered in 1983, there was a burst of optimism about possible vaccines, but HIV is different from most viruses for which vaccines have been developed and presents special challenges. The body mounts an early immune response to acute HIV infection but lasting immunity does not develop and the immune system eventually is destroyed.

HIV is perhaps the most genetically variable virus yet discovered. HIV-1, the predominant viral group in most of the world, differs greatly from HIV-2, the viral group responsible for AIDS in West Africa. Worldwide, there are at least nine distinct subtypes of HIV-1. Within the subtypes the genetic diversity of HIV is vast and any given population of virus within a host includes a large proportion of defective viral genomes. An asymptomatic patient might have at least one million genetically distinct variants of HIV; an AIDS patient might have

one hundred times that number. The source of the variation lies in the enzyme *reverse transcriptase* (described above) which has no "editing mechanism" to correct the errors in transcription which occur during viral reproduction. Thus, a vaccine effective against one strain of HIV will not necessarily confer immunity against the mixture of strains encountered in nature.

Experimental animals ("animal models") are needed for vaccine development, as well as for study of the disease process in AIDS. The ideal animal model would be an inexpensive laboratory animal in which HIV induces an AIDS-like condition. At present, there is no such model. Chimpanzees can be infected with HIV-l, but they do not develop AIDS, although their use is held to be valuable for vaccine development. The simian immunodeficiency virus (SIV) is related to HIV, and is very closely related to HIV-2. SIVs occur naturally in a number of African nonhuman primates but the virus is not normally pathogenic. SIV will, however, cause an AIDS-like condition in macaques, a simian group that includes the familiar rhesus monkey.

There are various types of HIV vaccine currently under development. The standard approach is the use of a *prophylactic* vaccine to prevent individuals becoming infected. Another approach is the use of a *therapeutic* vaccine to modify the disease in infected persons. One candidate prophylactic vaccine, produced by MicroGeneSys Inc. in the United States, and based on the gp160 precursor envelope glycoprotein molecule, had been slated for clinical trials in the United States, although the evidence supporting its effectiveness was controversial. In January 1995, the proposed $20-million trial of the microGeneSys "gp160 vaccine" was cancelled; the money was to be rolled into a fund for general research on HIV vaccines. Another approach is to develop a vaccine to prevent transmission of HIV from mother to fetus during pregnancy, an important consideration since more women are becoming infected with the virus.

There are two classic approaches to vaccine development for virus diseases. First, there is the use of a live virus that has been genetically altered, or "attenuated," to eliminate its ability to cause disease. Examples include vaccines to prevent polio and measles. This option has some potentially serious safety problems with HIV. The virus, as noted, mutates extremely rapidly and is known to recombine with other HIV strains, and potentially with other viruses, raising the possibility that the altered virus could regain its pathogenicity. Further, because there is no reliable

animal model in which to study HIV disease, an attenuated strain of the virus cannot be tested for pathogenicity.

Vaccines also may be based on inactivated, or "killed," whole virus. Testing of inactivated SIV vaccines in nonhuman primates has yielded some success in producing a protective response, but the protection has been brief and has been effective only against virus delivered by intravenous inoculation. There is also no evidence that any such HIV vaccine has generated the cytotoxic-T-lymphocyte response that is believed to be necessary for successful immunity to HIV.

A number of novel approaches to vaccine development are also being pursued with HIV/AIDS. Recombinant DNA (rDNA) technology is being used to produce large quantities of viral proteins and peptides, and even viral genes, which can be used as immunogens for vaccine production. Other new approaches include the use of various attenuated microorganisms, such as the vaccinia virus, containing an HIV gene encoding an HIV protein.

On 16 December 1994, the WHO announced that the first major human tests of AIDS vaccines will be carried out with heterosexual male drug users in Thailand and homosexual men in Brazil as the key volunteers. Two vaccines will be tested, both described as "gp120 subunit" vaccines. The designation "gp120" refers to a subunit of the envelope glycoprotein produced by the virus. The vaccines are specific for the HIV-1, subtype B virus strain which is found in Thailand and in the Caribbean and Latin America, but not in Africa. The vaccines have been shown to be safe for humans on the basis of small-scale trials in Europe and the United States. As many as 20,000 persons may take part in the trials, which are scheduled to begin within about two years. Dr. Peter Piot of Belgium will head the program. Recent research suggests, however, that the present generation of gp120 immunogens may not be effective against HIV-1 and that the costly vaccine tests currently planned by WHO should possibly be reconsidered.

In January 1995, an advisory committee recommended to the United States Food and Drug Administration that a therapeutic HIV vaccine should be allowed to move forward with an expanded clinical trial. The vaccine is not intended to prevent HIV infection but to halt, or at least delay, the deterioration of the patient's immune system. The vaccine is produced by the Immune Response company of Carlsbad, California. Opinion on the advisory committee was

divided on the issue, but the urgency associated with AIDS tipped the balance of opinion toward the trial.

In summary, much research will be needed to surmount the numerous problems that exist with HIV vaccines. In animal studies, vaccine protection lasts only for a short period and only against a virus identical to the one used to make the vaccine. This is a major problem, given the huge genetic variation among HIV populations: vaccines will have to provide immunity against the extreme genetic diversity of HIV observed in humans, a property known as *cross-reactivity*. It remains to be determined whether a special type of immunity is required to protect against mucosal exposure to HIV, such as would occur during sexual intercourse, as opposed to exposure through the blood stream. Also, protective immunity will need to be achieved against both cell-free and cell-associated virus particles since humans are rarely infected by cell-free virus.

Finally, the trials of any prophylactic HIV vaccine will be both difficult and controversial. To provide a "good" test of vaccine efficacy, an unprotected control group would have to be involved. The prospect of using such a group, without doing everything possible to prevent their becoming infected by the virus, raises very difficult ethical and moral issues.

F. Anti-HIV Drugs

The most publicized news coming out of the XI International Conference on AIDS was in regard to the recent successes that have been achieved in combating HIV by means of combination therapies consisting of two to four anti-HIV drugs given at one time. There is now a good indication that HIV infection will become a controllable chronic condition, and there is also the hope that a real cure may actually be possible in the future.

The genetic material of HIV contains nine genes, three of which code for essential enzymes. The first enzyme, reverse transciptase (RT), copies the viral RNA into the more common genetic material DNA. The second enzyme, integrase, snips the host's DNA and inserts the viral DNA sequence. Thus, through the normal operations of the host cell, the HIV sequence is read and translated into a long HIV protein strand.

Finally, the third enzyme, protease, cuts the protein strand at the correct points releasing all the protein subunits needed for the virus to self-assemble a new virus particle. In this manner, one infected CD4 cell can produce and release hundreds of new HIV particles.

The focus of anti-HIV drug development has been the design of drugs that specifically target the function of one of these enzymes. To date, most work has focused on two classes of drugs to defeat RT. The most common RT drugs, the nucleoside analogues, include AZT, ddI, ddC, 3TC, and d4T. In addition, there is also a group of non-nucleoside RT inhibitors, of which nevirapine, loviride, and delavirdine have been studied in most detail. There has also been some success in developing drugs to inactivate the protease enzyme. The major protease inhibitors include saquinavir, ritonavir, indinavir and nelfinavir. As yet, only a few drugs have been designed to interfere with integrase activity. These anti-integrase drugs, as well as a number of additional RT and protease inhibitors, are in the early stages of testing. By the year 2000, it is expected that there may be as many as 20 anti-HIV drugs that can be used in a large number of effective therapeutic combinations.

Since the first anti-HIV drug, AZT, came on to the market, the HIV virus has been able to defeat drug challenges by developing drug-resistant mutants. It has been estimated that each time HIV genetic material is duplicated, at least one, and perhaps even two or more, duplication mistakes are made. Every progeny virus that is different from the parent virus is a mutant. Some mutations are deleterious to the virus, making it less infectious or able to replicate; some mutations may benefit the virus; however, the vast majority of mutations have little or no effect. Due to the rapid rate of viral reproduction and the huge quantity of virus that may be present in the body, a few viral particles that are resistant to a specific drug may already exist in the body, even though the virus has never come in contact with that drug. When this happens, the drug may kill off the susceptible virus and the amount of virus in the blood (viral load) will drop dramatically. The resistant virus, however, is given a selective advantage; after a few months, it proliferates and previous viral levels are again attained. Alternatively, no

resistant mutants may be present, but the anti-HIV drug may not completely suppress viral replication. Viral load will drop, but a low level of viral reproduction continues and eventually a drug-resistant mutant appears and proliferates.

Mathematical analyses have shown that drug resistance to monotherapy can arise in only a few months. There is also a high possibility of a double mutation that results in drug resistance to combined two-drug therapy; however, there is an extremely low to negligible chance of a triple or quadruple mutation that would lead to drug resistance to combination therapies of three or more drugs. If HIV is challenged with high doses of three or more drugs, viral replication should be completely arrested so that reproduction cannot take place and triple or quadruple mutations cannot accumulate over time. It is now recommended that aggressive combination therapy be initiated as soon after initial infection as possible, before the immune system has been severely degraded and while the viral load is still relatively low and a wide variety of mutants have not yet accumulated.

It is now recognized that any combination of drugs should include both AZT and 3TC. AZT is a very potent anti-HIV drug. 3TC is less potent; however, the 3TC-AZT combination acts as a toggle switch against resistance. AZT resistance may arise, but 3TC keeps viral replication in check until resistance to it occurs. Luckily, the mutation that confers resistance to 3TC is the reverse of the mutation that gave AZT resistance, and the HIV becomes susceptible to AZT again. AZT and 3TC combined with ddI or the non-nucleoside RT inhibitor, nevirapine, have been found to reduce viral load to nearly non-detectable levels; however, even better results may be possible if AZT and 3TC are combined with a protease inhibitor. On their own, the protease inhibitors have been found to be very potent against HIV replication; however, resistant mutants quickly arise. Resistance does not appear to be a problem when optimum levels of protease inhibitor, AZT and 3TC are used. For example, in clinical trials, the continued use of a combination of indinavir, AZT and 3TC resulted in a sustained drop in viral load below detection level and a sustained gradual increase in CD4 count.

It is theorized that an early aggressive attack on HIV will stop replication, allow the immune system to heal, and, over time, allow the body to clear itself of virus. There is some indication that severely damaged immune systems may not completely heal, but some work has shown that CD4 replenishment can be encouraged by interleukin-2 therapy. No one yet knows how long it will take to clear HIV from the body, if indeed this is possible. Some long-lived body cells can function for three years before they are replaced and dormant HIV might shelter in them. In addition, some clinicians fear that dormant HIV might shelter indefinitely in certain specialized nerve cells or in the brain. Accordingly, only trial and error experimentation in humans will tell when or if combination therapy can be terminated. On a positive note, no evidence of HIV was seen when lymph node biopsies were conducted on six patients after 78 weeks on a combination of AZT, 3TC, ddI, ddC and interferon-alpha therapy.

In spite of the good news, it is estimated that combination therapy will cost more than $13,000 per patient per year, which will put a financial strain on the health care budgets of developed nations. This is a minor concern, however, when compared to the plight of those living with HIV in developing nations. The developing countries of the world contain 90% of all HIV infections, and the poor who live there have no hope of ever affording anti-HIV therapies. Unless the cost of anti-HIV drugs can be drastically reduced, the recent successes in combination drug therapy will have virtually no effect in stemming the world AIDS pandemic.

G. The Krever Commission

In September 1993, following the annual meeting of federal-provincial-territorial ministers of health in Edmonton, it was announced that the alleged failures of the Canadian blood system to protect Canadians adequately from HIV infection would be the subject of an inquiry. The commissioner for the inquiry would be Mr. Justice Horace Krever, Justice of the Ontario Supreme Court and Member of the Ontario Court of Appeal. The inquiry, which began 22 November, was conducted pursuant to Part I of the federal *Inquiries Act*.

On 14 February 1994, testimony began at the inquiry into Canada's blood system. Public hearings were held in every province. Prior to the start of the public hearings, however, Canada's deputy health ministers suggested that major changes be made to the blood system and recommended that the Canadian Red Cross no longer have control of purchases of blood products. A report by the deputy ministers suggested that the Canadian Blood Agency assume this responsibility.

The Krever Inquiry's 485-page Interim Report was released on 24 February 1995. In addition to making recommendations for improving the safety of Canada's blood system, the report recommended that hospitals should contact individually the estimated 3.5 million Canadians who had received blood transfusions between 1978 and 1985, to inform them of the risks of HIV infection from the transfusions and of the advisability of being tested.

In December 1995, as required by section 13 of the *Inquiries Act*, Judge Krever issued notices to a number of individuals informing them that the final Commission report might assign blame to them. The right of the Commission to assign blame was challenged in the Federal Court of Canada by the Canadian Red Cross, the federal government, six provinces, five pharmaceutical companies, and a number of individuals. In June 1996, Mr. Justice John Richard allowed allegations of potential misconduct to stand against 17 Red Cross and federal officials; however, he forbade the inquiry to assign blame to 47 other people, including former health ministers and senior bureaucrats. Because of the holdup caused by the court challenge, Judge Krever was unable to submit the Commission's final report on time. The Commission has been granted an extension and the report is due 30 April 1997.

When the Commission was established, its mandate was to investigate and assess the problems and shortcomings of the Canadian blood system and make recommendations. The Commission's recommendations were then to be used by the federal and provincial governments to reorganize the Canadian blood system to help ensure that such a tragedy would not occur again. Due to the many delays experienced by the Commission, federal, provincial and territorial health ministers felt the safety of the Canadian blood supply could not wait until receipt of the final report. On

10 September 1996, these ministers announced that a new national authority would be established within one year, at arm's length from all governments, to operate the blood system. The ministers stated that this direction takes into account the interim report of the Commission, and that this timing will also allow consideration of further recommendations from the Commission.

PARLIAMENTARY ACTION

Several reports on AIDS have emanated from Parliament. In May 1986, the House of Commons Standing Committee on National Health and Welfare tabled a report entitled *AIDS in Canada*. In June 1990, the Ad Hoc Parliamentary Committee on AIDS released its report, *Confronting A Crisis*. In November 1992, the House of Commons Standing Committee on Health and Welfare, Social Affairs, Seniors and the Status of Women held public hearings in the form of a round table discussion with the Ad Hoc Parliamentary Committee on AIDS to focus on renewed federal funding for the national AIDS strategy.

On 26 November 1992, the Sub-Committee on Health Issues of the House of Commons Standing Committee on Health and Welfare, Social Affairs, Seniors and the Status of Women commenced public hearings on a "study of HIV-infected blood and other related matters." The Sub-Committee's report, *Tragedy and Challenge: Canada's Blood System and HIV*, was tabled in the House of Commons in May 1993 and made nine recommendations. The principal recommendation was for a public inquiry into Canada's blood system. The efficiency and safety of the system was the primary focus of the report, which included a full examination of the events of the 1980s when the blood supply became contaminated by HIV.

The House of Commons Sub-Committee on HIV/AIDS was formed in December 1994, and its first report, *A Study of the National AIDS Strategy: Report of the Sub-Committee on HIV/AIDS*, was presented to Parliament one year later. The report contained 23 recommendations aimed at strengthening the response of the federal government to the AIDS epidemic. The Sub-Committee then examined the issue of compassionate access to experimental drugs for people who are catastrophically ill and,

in October 1996, submitted their findings to Parliament in the report *Compassionate Access to Investigational Therapies: Second Report of the Sub-Committee on HIV/AIDS*. This document made eight recommendations focused on developing mechanisms to liberalize access to unproved drugs while still maintaining the rigour of clinical drug trials. In October 1996, the Sub-Committee began an investigation of how poverty, discrimination and other factors may lead to marginalization of affected groups and thus limit the effectiveness of the National AIDS Strategy.

CHRONOLOGY

June 1981 - AIDS was first reported by the Centers for Disease Control (CDC) in the United States and was incorrectly attributed only to promiscuous homosexual activity among males.

February 1982 - AIDS was first reported in Canada.

June 1982 - CDC reported that 20% of the U.S. patients were heterosexual IV drug abusers of both sexes.

July 1982 - CDC reported that hemophiliacs had contracted AIDS through blood products.

May 1983 - AIDS virus, LAV (lymphadenopathy associated virus) was discovered in France.

September 1983 - National Advisory Committee on AIDS was established in Canada.

April 1984 - AIDS virus HTLV-III (human T-cell lymphotropic virus III) - believed to be the same as the LAV virus - was discovered in the U.S.A.

March 1985 - U.S. approval of the first commercial screening test for the presence of AIDS virus antibodies in blood.

May 1985 - Heat treatment for hemophilia blood complexes was initiated in Canada (100% in place by June 1985).

November 1985 - Blood screening of donated blood for AIDS virus antibodies began in Canada.

1 May 1986 - Minister of National Health and Welfare announced a $39-million, five-year plan to support activities dealing with AIDS in Canada.

8 June 1988 - The Minister of National Health and Welfare allocated an additional $ 129 million over five years to the federal government's AIDS program.

16 October 1989 - The Minister of National Health and Welfare announced that a new HIV Clinical Trials Network would be developed in Canada by the University of British Columbia at St. Paul's Hospital in Vancouver. The Network will improve the access of patients and physicians to clinical trials of drugs and vaccines for treatment of AIDS and HIV infection.

24 April 1990 - The Minister of National Health and Welfare announced the federal government's intention to establish a National Treatment Registry for persons with AIDS. The Registry would be known as the Treatment Information System for AIDS and HIV Infection (TISAH) and be based at the University of Toronto.

28 June 1990 - The Minister of Health and Welfare, Mr. Beatty, presented the National Strategy on AIDS. The Strategy did not include any new federal funding; existing funds were re-allocated.

October 1990 - Anonymous blood testing of 67,078 newborn babies born in Ontario between October 1989 and July 1990 showed that 21 tested positive for HIV antibodies, for an indicated infection rate of 3.1 per 10,000. This rate was about double that anticipated. Where a blood test indicates that the mother is infected with HIV, the newborn has a 30-50% probability of being infected also.

30 October 1991 - The Minister of Health and Welfare, Benoît Bouchard, announced that the Federal Centre for AIDS would be phased out and its duties assumed by other units of the department. A national AIDS Secretariat was created to serve as the departmental focal point of HIV/AIDS issues. AIDS surveillance and epidemiological research, and biomedical/laboratory research would be carried out by the Laboratory Centre for Disease Control. The Health Services and Promotion Branch would handle AIDS education and prevention strategies and funding for national and community-based groups, and for non-governmental organizations. A new unit of the Branch would be created to address care and treatment issues.

January 1992 - The Ontario Ministry of Health set up anonymous HIV-testing centres across the province. The program was to cost $600,000 and be part of a $2.1 million AIDS program announced by the government in October 1991. Many AIDS workers believed that the anonymity of the testing would encourage persons at risk to come forward to be tested.

July 1992 - At the Eighth International AIDS Conference in Amsterdam, a topic of major interest was the possibility that AIDS, or a condition similar to AIDS, may occur in the absence in infection by either HIV-1 or HIV-2, the viruses believed to be responsible for the disease.

15 April 1993 - The Hospital for Sick Children in Toronto announced that it would notify the families of children who received blood transfusions between 1980 and 1985 that they might have been exposed to HIV. It was estimated that some 17,000 former patients might be involved. The program was to start by sending letters to some 1,700 families of former pediatric heart patients. The program was to be expanded if the initial effort was successful. In mid-June, the Hospital announced that six former patients had been found to be HIV-positive.

24 November 1993 - The Hospital for Sick Children in Toronto announced that 17 of the 1,700 pediatric heart patients contacted in April 1993 had tested positive for HIV. This 1% infection rate was higher than had been expected. The hospital set up a "hot line" for parents seeking information on transfusions during the 1980-1985 period.

7 June 1994 - At its annual meeting in Halifax, the Canadian Hospital Association announced that it would develop a national campaign urging persons who had received blood between 1978 and 1985 to be tested for HIV. The campaign would involve individual hospitals, and the federal and provincial governments. Three weeks later, the Ontario Hospital Association launched a province-wide campaign urging blood recipients from the period in question to be tested for HIV.

25 June 1994 - After two years of discussion and debate, the Canadian Red Cross Society formally announced plans to construct a $150-million blood-processing plant near Halifax. The plant would be run jointly by the Red Cross and Miles Incorporated, a subsidiary of the German pharmaceutical company, Bayer AG. The plant was scheduled to open by 1997.

July 1994 - A paper in the journal *Science* quoted a WHO estimate that, worldwide, at least 3 million people have developed AIDS and that, cumulatively, at least 15 million people have been infected by HIV. It was estimated that, cumulatively, by the year 2000, 30 to 40 million people would have been infected by HIV since the start of the epidemic.

19 July 1994 - A Reuter report in the *Globe and Mail* stated that the U.S. National Task Force on AIDS Drug Development had been told that some medical firms planned to terminate their AIDS research if the current approach to finding a therapy proved fruitless. The most recent avenue of research focused on "protease inhibitors"; protease is an enzyme essential to the replication of HIV. This announcement was in line with information presented at the 10th International Conference on AIDS (see below).

7-12 August 1994 - The 10th International Conference on AIDS was held in Yokohama, Japan, the first ever in Asia. The conference included few reports on new results of AIDS drugs or therapies, and no indication that vaccine development was a realistic hope for the near future. One important announcement was that zidovudine (AZT), given to HIV--positive pregnant women, can protect their babies from infection. The dominant theme of the conference was that more resources needed to be directed to basic research on the virus and on the human immune system. There was an indication that the U.S. National Institutes of Health might divert some funds away from clinical trials of AIDS drugs towards basic research, although vaccine research and testing might not be affected. The conference organizers planned to stage the conference every two years in future, instead of continuing the annual format.

31 August 1994 - A report in the *Globe and Mail* stated that the federal Laboratory Centre for Disease Control "estimates that in Canada between 940 and 1,440 persons became infected due to transfusion in the period 1978-85" and that as many as 245 persons might still be unaware of their HIV-positive status. The figure of 1,440 was described as the "worst case estimate."

16 December 1994 - The WHO announced that the first major human tests of AIDS vaccines would be carried out with heterosexual male drug users in Thailand and homosexual men in Brazil as the key volunteers.

1 May 1995 - The Secretary-General of the Canadian Red Cross Society stated that, although Canada's blood supply today is as safe as that of any

developed country, blood recipients still have approximately a one in 50,000 chance of contracting HIV through blood and blood products. This continuing small risk of infection is in part due to the fact that a blood donor may be infected by HIV but test negative for HIV antibodies at the time of donation.

29 June 1995 - Health Minister Diane Marleau announced funding for a national HIV/AIDS Treatment Information Network which will be administered by CATIE, the Community AIDS Treatment Information Exchange of Toronto. The network will provide information on the diagnosis and treatment of HIV and AIDS, on clinical advances in the field, on drug and non-drug therapies, on medical and complementary therapies, and on where to obtain care. Health Canada will provide $4.9 million over three years to establish the network, which will be operational by the end of 1995.

7-12 July 1996 - Vancouver hosted the XI International Conference on AIDS. Data presented at this conference showed that it should be possible to transform HIV/AIDS from a terminal disease to a chronic controllable condition through the use of "drug cocktails" of three or more anti-HIV drugs.

10 September 1996 - Federal, Provincial and Territorial Ministers of Health agreed to establish, within one year, a new national authority to operate Canada's blood system. The new blood authority will operate at arm's length from all governments and will be responsible for managing all aspects of an accountable and fully integrated blood system. Quebec has decided to establish a separate agency of its own.

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